

## REMARKS

Claims 1-14, 17 and 67-68 and 70-72 are pending. Applicants have amended claim 1 to incorporate the subject matter of claim 69, which is now cancelled. Additional support for the amendment to claim 1 appears in the specification at, e.g., page 8, lines 17-18 and 28-29, page 14, lines 26-27, and page 21, lines 8-10. No new matter has been added.

### Rejections under 35 U.S.C. § 103

Claims 1-6, 17, 67 and 68 remain rejected for obviousness over Kallioniemi *et al.* U.S. Publication No. 2002/0132246 (“Kallioniemi”) in light of McGill *et al.* U.S. Patent No. 5,658,730 (“McGill”) (see page 2, paragraph 4A of the Office Action). In addition, claims 1-6, 12-14, 17 and 67-72 are newly rejected as obvious over Kallioniemi in light of McGill and Pollack *et al.* Nature Genetics 23:41-46 (1999) (“Pollack”) (see page 8, paragraph 13 of the Office Action).

These rejections are considered together, as all are based on the combination of Kallioniemi and McGill. The rejections are traversed to the extent they are applied to the claims as amended.

Applicants have amended claim 1, from which depend claims 2-6, 17, 67 and 68, to specify that the fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and that both strands are labeled with a detectable moiety.

The combination of Kallioniemi, McGill does not produce, nor does it provide a motivation for, an invention with these features. As noted by the Examiner, Kallioniemi does not describe an array-based comparative genomic hybridization (CGH) method in which the labeled genomic DNA fragments are less than 200 bp (see page 5, paragraph 2 of the Office Action).

McGill does not describe a method using genomic fragments that are less than 200 bp, and which include both strands of a double-stranded genomic DNA fragment, as well as including at least 30% repetitive sequences. Rather, it is cited for describing a method for detecting amplification in a unique region of chromosome 8 (col. 4, lines 2-11):

Surprisingly a unique DNA segment of this probe was further localized to the 8q24.1-24.2 region, and was shown to be diagnostic for metastatic progression of prostate cancer. It is quite likely that one or more unique members of this probe family will be useful for the isolation of particular subregions of 8q24.1-24.2, and the identification of specific gene(s) associated with prostate cancer. Such unique probes will provide the basis for diagnostic kits identifying metastatic tumor progression in these patients.

A probe that includes at least 30% repetitive sequences could not localize uniquely to the chromosomal region identified by McGill. Thus, one cannot turn from Kallioniemi to McGill to arrive at the claimed invention because the latter reference does not describe short (i.e., less than 200 bp) fragments from double-stranded including at least 30% repetitive sequences. There is no suggestion in either reference, singly or in combination, of a method that uses genomic DNA that is provided in a fragment that double stranded, includes at least 30% repetitive sequence, is less than about 200 bases, and which results in less aggregating hybridization or less background relative to hybridization of the target genomic nucleic acid to the probes using target nucleic acids with labeled fragments of length greater than about 200 bases.

Pollack does not cure the deficiencies of Kallioniemi and McGill. Pollack teaches that labeling efficiency is increased by lessening the size of a genomic fragment. However, Pollack does not teach the sizes of these fragments or how much in size these fragments should be reduced. Further, Pollack does not teach double stranded fragments including at least 30% repetitive sequences or fragments of 200 bp or smaller. Pollack also does not teach that smaller fragments result in less aggregating hybridization or less background relative to hybridization.

For at least these reasons, claims 1-6, 12-14, 17 and 67-72 are further non-obvious over the combination of Kallioniemi, McGill and Pollack.

Claim 72 (which depends from claim 1 and from which depends claims 67-69) additionally requires that the fragments of genomic acid include nucleic acids from all of one or more chromosomes of the organism. There is no suggestion in either Kallioniemi, McGill or Pollack of a method using a short (less than about 200 bases) probe with the sequence complexity required by claim 72, and which results in less aggregating hybridization or less background relative to hybridization of the target genomic nucleic acid to the probes using target nucleic acids with labeled fragments of length greater than about 200 bases. Kallioniemi and Pollack, as noted above, do not discuss probes less than about 200 bases, and the short probes

described in McGill are comparatively low complexity oligonucleotides based on defined sequences from human chromosome 8. However, there is no suggestion in any reference that labeling a fragment with a complexity corresponding to one or more chromosomes of an organism. For at least these reasons, new claim 72 and dependent claims 67-69 are further non-obvious over the combination of Kallioniemi, McGill and Pollack.

Claims 7, 8 and 10 remain rejected as unpatentable for obviousness over Kallioniemi, McGill, and Anderson et al., Nucl. Acids Res. 9:3015-27, 1991 ("Anderson") (page 3, paragraph 4B of the Office Action), and claims 7, 8 and 10 are also newly rejected as unpatentable for obviousness over Kallioniemi, McGill, Pollack and Anderson. (see page 11, paragraph 14 of the Office Action). Both rejections are traversed to the extent they are applied to the claims as amended.

Claims 7, 8, and 10 depend from claim 1 which, for the reasons provided above, is non-obvious over the combination of Kallioniemi and McGill and Kallioniemi and McGill and Pollack. Anderson is cited for describing a method for fragmenting genomic DNA using DNase; however, it fails to overcome the deficiencies of Kallioniemi, McGill and Pollack described above.

Claim 9 remains rejected as unpatentable for obviousness over Kallioniemi, McGill, Anderson, and Waggoner, US Patent No. 5,268,486 ("Waggoner") (see page 3, paragraph 4C of the Office Action). Claim 9 is also newly rejected as unpatentable for obviousness over Kallioniemi, McGill, Anderson, Pollack and Waggoner. (see page 12, paragraph 15 of the Office Action).

Claim 9 depends from claim 8, which for the reasons provided above is non-obvious over the combination of Kallioniemi, McGill, and Anderson or Kallioniemi, McGill, Pollack and Anderson. Waggoner is cited for describing luminescent cyanine dyes; however, it, too fails to overcome the deficiencies of Kallioniemi, McGill, and Anderson or Kallioniemi, McGill, Pollack and Anderson.

Claim 11 remains rejected as unpatentable for obviousness over Kallioniemi, McGill, Anderson, and Ordahl, Nucl. Acids Res. 3:2985-99, 1976 ("Ordahl") (see page 3, paragraph 4D of the Office Action). Claim 11 is also newly rejected as unpatentable for obviousness over

Kallioniemi, McGill, Anderson, Pollack and Ordahl. (see page 12, paragraph 16 of the Office Action).

Claim 11 depends from claim 1, which for the reasons provided above, is non-obvious over the combination of Kallioniemi and McGill or Kallioniemi, McGill and Pollack. Anderson has been discussed above. Ordahl is cited for describing a method for fragmenting DNA using a French press. However, there is no suggestion in this reference of the invention of claim 1; thus it, too fails to overcome the deficiencies of Kallioniemi, McGill, and Anderson or Kallioniemi, McGill, Pollack and Anderson.

Applicants request reconsideration and withdrawal of the rejections for obviousness.

#### **Rejections under 35 USC § 112, second paragraph**

Claims 1-14, 17, and 67-72 are rejected as indefinite, on various grounds. The claims have been amended to remove the language objected to by the Examiner. Accordingly, this rejection can be withdrawn.

#### **Rejections under 35 USC § 102(b)**

Claims 1-6, 12, 13, 70 and 71 are rejected as anticipated by Cai et al., Genomics 54:387-397, 1998 ("Cai"). The rejection is traversed to the extent it is applied to the claims as amended.

Claim 1, from which the remaining claims subject to the rejection depend, have been amended to specify that the probes contacting the nucleic acid probes include both strands of a double-stranded genomic DNA fragment, and include at least 30% repetitive sequences.

Cai does not describe a method that uses both strands of a double-stranded genomic DNA fragment. Instead, it describes a method that hybridizes specifically designed multiplex single-stranded oligonucleotides to members of a BAC library (see, e.g., paragraph bridging pages 389 and 390).

Cai also fails to describe a probe that includes at least 30% repetitive sequences. Rather, this reference explains that its probes recognize unique sequences (paragraph bridging pages 389-390):

The key to the success of running this row and column multiplex probe hybridization on a BAC genomic library largely relies on the design of probes with similar hybridization kinetics and unique specificities.

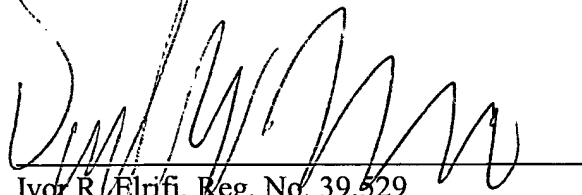
Cai therefore does not describe all the features of claim 1 as amended and thus does not anticipate the claim, or the claims that depend from claim 1. Applicants request reconsideration and withdrawal of the rejection.

On the basis of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance.

A petition for extension of time accompanies this response. If the Examiner has any questions regarding these amendments and remarks, the Examiner is encouraged and invited to contact the undersigned at the telephone number provided below.

The Commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 27476-504.

Respectfully submitted,



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